cerebral blood flow in the subject and thereby treat Alzheimer's disease in the subject.--

REMARKS

Claims 1-16 are pending in the subject application. Applicants have hereinabove canceled claim 3 without prejudice or disclaimer to applicants' rights to pursue the subject matter of this claim in a later-filed application. Further, applicants have amended claims 2 and 16. Support may be found *inter alia* in the specification as follows: claim 2: page 7, lines 12-13; claim 16: page 7, lines 16-22. Claims 1-2 and 4-16 do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1-2 and 4-16 will be pending.

Drawings

The Examiner stated that the subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. The Examiner stated that Applicant is required to furnish a drawing under 37 CFR 1.81. The Examiner stated that no new matter may be introduced in the required drawing.

In response, applicants will consider providing drawings upon the indication of allowable subject matter.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-16 under 35 U.S.C. 112, first paragraph, alleging that the specification, is enabling for methods

of decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a transgenic mouse which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met671Leu, (TG APP sw +/- mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE) but that it does not reasonably provide enablement for methods of decreasing cerebral vasoconstriction, ameliorating neurovascular stress or treatment of amyloid angiopathy in all transgenic non-human animals by administration of any inhibitor of RAGE. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner stated that the claimed invention is directed to a method for decreasing cerebral vasoconstriction in a subject suffering from chronic or acute cerebral amyloid angiopathy which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) to inhibit transcytosis of amyloid β (Aβ) peptides across the blood-brain barrier in the subject (claim 1). The Examiner stated that the claimed invention is further directed to a method for ameliorating neurovascular stress in a subject, comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 12). The Examiner stated that the claimed invention is additionally directed to a method of treating amyloid angiopathy in a subject comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 16). The Examiner stated that in

particular, the elected inhibitor of RAGE is soluble (sRAGE) and the elected subject is a transgenic non-human animal. The Examiner stated that the specification teaches that administration of an inhibitor of RAGE can be used to treat subjects suffering from chronic or acute cerebral amyloid angiopathy, ameliorate neurovascular stress, or in the treatment of amyloid angiopathy (see p. 7. 1st paragraph, p. 8, paragraphs 1 and 3). The Examiner stated that the specification specifically teaches the blocking of RAGE in wild-type mice infused with synthetic amyloid-beta (Aβ) peptides by the use of an antibody against RAGE (α-RAGE), and soluble RAGE (sRAGE), which resulted in the suppression of binding and uptake of Aβ in relation to the vessel wall, and inhibited Aβ-induced cellular stress (see Example 1, and particularly p. 34). The Examiner stated that the specification teaches that Aβ transport to the brain was significantly inhibited by α-RAGE and abolished by sRAGE and that several other molecular reagents were used to test effects on blood brain barrier (BBB) transport or the binding of Aβ (see p. 32). The Examiner stated that the specification teaches that transgenic mice that overexpress mutant Aβ precursor protein (APP) (TG APP sw+/- mice) have a significant decrease in basal cerebral blood flow (CBF) values, and that infusion of α-RAGE increased the CBF in these mice. The Examiner stated that the specification teaches that systemic administration of α-RAGE to these transgenic mice ameliorated cellular stress in the brain (see p. 33, lines 11-29). The Examiner stated that the specification further teaches that an acute model in mice that had Aβ-induced cellular stress and sustained reductions in CBF was

blocked by circulating α-RAGE, and in TG APP sw +/- mice, CBF was reduced by circulating α-RAGE in a dose-dependent fashion (see Example 2). The Examiner stated that although the specification does not explicitly teach the use of sRAGE administration to the TG APP sw +/- mice, Morser et al. (WO 97/39121, 23 October 1997) teach that both antibodies to RAGE and soluble RAGE are capable of blocking or inhibiting the interaction between RAGE and its ligands (AGEs) in such diseases as diabetes and Alzheimer's disease (see p. 9, 2nd paragraph and Examples 2 and 4). The Examiner stated that to this end, one would have a reasonable expectation of success in using sRAGE to increase CBF and ameliorate cellular stress in TG APP sw+/- mice. The Examiner stated that as such, the claimed invention is enabled for methods for decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a TG APP sw +/- mouse by the administration of sRAGE as indicated above. However, the Examiner alleged that the specification fails to teach methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in any other transgenic non-human animal other than the exemplified TG APP sw +/- mice. Additionally, the Examiner alleged that specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic non-human animal as claimed, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce all transgenic animals which over-express mutant human Aβ precursor protein. The Examiner alleged that this is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. The Examiner

alleged that while the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. The Examiner alleged that for instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The Examiner alleged that the individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. The Examiner alleged that this observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." The Examiner stated to see page 61, last paragraph. The Examiner stated to see also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g., specific promoters, presence or absence of introns, etc. The Examiner alleged that as such guidance is lacking in the instant specification, it fails to feature any correlation between the over-expression of a mutant human amyloid beta precursor protein transgene and/or mis-

expression of the endogenous gene in any host animal, and, thus, a specific resulting disease phenotype. Furthermore, the Examiner alleged that without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). The Examiner alleged that this observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The Examiner alleged that the same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. The Examiner stated to see also Ebert et al. (Molecular Endocrinology, 1988). The Examiner alleged that this observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgeneis in the rat and larger mammals. The Examiner stated that Mullins et al state that "a given construct may react very differently from one species to another." The Examiner stated to see page S39, Summary. The Examiner stated that Wall et al report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." The Examiner stated to see page 62, first paragraph. The Examiner stated that Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting,

resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). The Examiner stated that Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different transacting factors in these other species (paragraph bridging pages 238-239). The Examiner alleged that given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of even one transgenic animal whose genome comprises a mutant human amyloid beta precursor protein transgene, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing an mutant human amyloid beta precursor protein transgene, the levels of the transgene product, the consequences of that production, and therefore, the resulting phenotype. The Examiner alleged that with specific regard to Claim 16, the claim encompasses treatment of amyloid angiopathy. The Examiner stated that 'treatment' encompasses complete amelioration of symptoms associated with Alzheimer's disease, and not necessarily a mere increase in cerebral blood flow, as such increase may not be sufficient to provide therapy in a subject with Alzheimer's disease, for example.

Specifically, the Examiner alleged that in view of the lack of guidance and direction in the specification for the use of sRAGE to decrease cerebral vasoconstriction or ameliorate neurovascular

stress in any other species other than TG APP sw +/- mice, the lack of guidance or teaching for the treatment of amyloid angiopathy in such mice, and the unpredictable and undeveloped state of the art with respect to transgene behavior in transgenic animals of all species, it would have required undue experimentation for one skilled in the art to carry out the claimed methods, animals and use thereof. The Examiner stated that no claim is allowed. The Examiner stated that claims 1-16 appear to be free of the prior art of record, in that prior art of record fails to teach or suggest the use of sRAGE to decrease cerebral vasoconstriction, ameliorate neurovascular stress or treat amyloid angiopathy in a subject.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the specification is enabled for decreasing cerebral vasoconstriction, ameliorating neurovascular stress, and treating Alzheimer's disease(hereinafter "AD") in a subject and that it would not have required undue experimentation for one skilled in the art to carry out the claimed invention.

State of the art of transgene behavior

Without conceding the correctness of the Examiner's position regarding the "unpredictable and undeveloped state of the art with respect to transgene behavior in transgenic animals of all species," but to expedite prosecution of the subject application, applicants have hereinabove amended claim 2. Claim 2 now recites in-part, "wherein the subject is a **human subject.**" In addition,

applicants have canceled claim 3 without prejudice or disclaimer to applicants' right to pursue the subject matter of this claim in a later filed application. Accordingly, the newly amended claim 2 and canceled claim 3 no longer recite that the subject is a **transgenic** non-human animal or that the transgenic non-human animal is a **transgenic** mouse and therefore obviates the Examiner's objection regarding the alleged limitations of transgenic technology. Applicants contend that these remarks obviate the Examiner's objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Treatment of amyloid angiopathy

In response to the Examiner's comments alleging a lack of guidance or teaching for the treatment of amyloid angiopathy in the present application, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 16 such that it now recites as follows: "A method for treating Alzheimer's disease in a subject which comprises administering to the subject an effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) activity so as to increase cerebral blood flow in the subject and thereby treat **Alzheimer's disease** in the subject." Accordingly, the newly amended claim 16 no longer recites a method to increase blood flow in the subject to treat "**amyloid angiopathy**" and therefore obviates the Examiner's objection to the alleged lack of guidance or teaching for the treatment of

amyloid angiopathy. Applicants contend that these remarks obviate the Examiner's objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Transgenic mouse data support treatment of AD in a human subject

Applicants contend that the state of the art of transgenic mouse models of AD-type pathology support the use of a RAGE inhibitor to decrease cerebral vasoconstriction and ameliorate neurovascular stress in such mice as a therapeutic model for treating AD in a human subject. Therefore, the specification and claims teach without undue experimentation the use of a RAGE inhibitor to reduce cerebral vasoconstriction and ameliorate neurovascular stress thereby treating AD in a human subject.

Various papers support the idea that transgenic mice with AD-type pathology may be useful for identifying methods of treatment of AD in a human subject.

In support, applicants attach hereto as **Exhibit B** a copy of a paper by Hsaio et al.(Science 274:99-102, 1996), entitled "Correlative Memory Deficits, Aβ Elevation, and Amyloid Plaques in Transgenic Mice" states that they have produced a strain of transgenic mice which overexpress the 695-amino acid isoform of human Alzheimer β-amyloid(Aβ) precursor protein and that the "correlative appearance of behavioral, biochemical, and pathological abnormalities reminiscent of Alzheimer's disease in these transgenic mice suggests new opportunities for exploring the pathophysiology and

neurobiology of this disease." See page 99, abstract. Specifically, the paper shows that transgenic mice expressing 5-fold and 14-fold increase in expression of the 695-amino acid isoform of human APP containing a lys670Asn, Met671Leu mutation had normal learning and memory in spatial reference and alteration tasks at three months of age but developed plaques and showed impairment by 9-10 months of age. See page 99, figure 1 and page 100, figure 2. The paper further states that their results "demonstrate the feasibility of creating transgenic mice with robust behavioral and pathological features resembling those found in AD." See page 102, column 1. Accordingly, the applicants contend that this paper shows that transgenic mice which overexpress human APP develop Aβ plaques and behavioral deficits similar to those observed in human AD subjects and therefore model AD in a human subject.

In further support, applicants also attach hereto as **Exhibit C** a copy of a paper by John Hardy(Proc. Natl. Acad. Sci. 90:2095-2097, 1997), entitled "The Alzheimer family of diseases: Many etiologies, one pathogenesis?" which states that mutations in the APP, PS1 and PS2 genes, singly or in combination, alter APP processing such that an increased amount of Aβ42 is produced causing AD-type pathology in cell culture, transgenic mice, and human subjects with PS-encoded Alzheimer's disease. See page 2095, first column. The paper further states that pathological analysis show that Aβ42 is deposited early and selectively in plaques that are characteristic of AD and that these *in vitro* cell culture and *in vivo* mouse data

"give a single, coherent picture of the pathogenesis of the disease" and "provide the strongest possible evidence that the amyloid cascade hypothesis for the etiology and pathogenesis of AD is correct." See page 2095, first column. The authors conclude by stating that with regards to the development of AD in humans, "we now know several causes of the disease(all genetic so far), and all of these causes have pointed toward the path of APP metabolism and deposition as being the early event in the disease pathogenesis." See page 2096, first column. Accordingly, applicants contend that this paper shows the following: 1)that an increased amount of Aβ42 in transgenic mice create plaques that are characteristic of AD; 2)an increased amount of Aβ42 is observed in human subjects with PS-encoded AD; and 3)that the causes of AD have pointed toward the path of APP metabolism and deposition causing plaque formation as being the early events in AD pathogenesis. Therefore, the applicants maintain that transgenic mice, such as the TgAPPsw+/- mice used in the present application, which exhibit an increase in Aβ42 and plaque formation provide a useful model for the treatment of AD in a human subject.

Applicants further attach as **Exhibit D** a copy of a paper by Marina R. Picciotto and Kevin Wickman(Physiol. Rev. 78: 1131-1163, 1998), entitled "Using Knockout and Transgenic Mice to study Neurophysiology and Behavior" which states that "mice have been generated that develop plaques and show behavioral consequences linked to mutant APP expression, establishing a connection between abnormal APP expression and cognitive impairment." See page 1154,

column 2. The paper further states that transgenic mice expressing human APP and fAD-linked PS1 mutants under the control of the hamster prion promoter exhibited significant Aβ42 overproduction in the brain and that these "mouse models have begun to identify the mechanisms underlying the pathology associated with Alzheimer's disease." See page 1155, column 1. Accordingly, the Picciotto and Wickman paper indicates that transgenic mice which abnormally express mutant APP develop plaques and behavioral hallmarks associated with AD in a human subject and therefore have begun to identify the mechanisms underlying development of AD in a human subject.

Applicants further attach as **Exhibit E** a paper by Schenck et al. (Nature 400:173-177, 1999), entitled "Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse" which demonstrate the effect of Aβ immunization on plaque load in transgenic mice with Alzheimer's disease-type neuropathologies and state "that such immunization reduced β-amyloid plaque formation and may be effective in treating Alzheimer's disease." See page 247, abstract. The paper also states that "the Aβ42-immunized mice never developed the neurodegenerative lesion that typify the progression of AD-type pathology in this model." See page 175, column 2. The paper further states that these data are the first report of "a clinically relevant treatment that reduces the progression of AD-like neuropathology in a transgenic animal model of the disease," and "that it is not unreasonable to expect that a similar reduction of neuropathology in AD patients would be of

clinical benefit." See page 177, column 1. Accordingly, applicants contend that this paper shows that the reduction of β-amyloid plaque treats AD-type pathology in a transgenic mouse model of AD and may therefore be effective in treating a human subject with AD.

In support, applicants further attach hereto as **Exhibit F** a copy of a paper by Weggen et al.(Nature 414:212-216, 2001), entitled "A subset of NSAIDS lower amyloidogenic Aβ42 independently of cyclooxygenase activity" which states that "epidemiological studies have documented a reduced prevalence of Alzheimer's disease among user of nonsteroidal anti-inflammatory drugs(NSAIDS)." The paper further states that two selective COX inhibitors, i.e. ibuprofen and indomethacin, have "reduced amyloid plaque pathology in a mouse model(Tg2576 transgenic mice) of Alzheimer's disease" and "seemed to slow the cognitive decline in [human] patients with Alzheimer's disease." See page 213, column 1 and page 214, column 1. Accordingly, applicants contend that this paper shows that a subset of NSAIDS treated AD-type pathology in transgenic mice and symptoms of Alzheimer's disease in human patients.

Accordingly, applicants contend that these papers demonstrate that the state of the art of transgenic mouse models of AD-type pathology support the use of a RAGE inhibitor to decrease cerebral vasoconstriction and ameliorate neurovascular stress in such mice as a therapeutic model for treating AD in a human subject.

Summary

In view of the foregoing remarks and amendments, applicant respectfully requests that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 1-2 and 4-18 .

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

12/20/01

John P. White Date
Reg. No. 28,678

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EXHIBIT A

--1. (Amended) A method for decreasing cerebral vasoconstriction in a subject suffering from [chronic or acute cerebral amyloid angiopathy] Alzheimer's disease which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) in an effective amount to inhibit transcytosis of amyloid β peptides across the blood-brain barrier in the subject, thereby decreasing cerebcral vasoconstriction in the subject.--

--2. (Amended) The method of claim 1, wherein the subject is a [transgenic non-human animal or a] human.--

--16. (Amended) A method for treating [Amyloid Angiopathy] Alzheimer's disease in a subject who suffers therefrom which comprises administering to the subject an effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) activity so as to increase cerebral blood flow in the subject and thereby treat [amyloid angiopathy] Alzheimer's disease in the subject.--